REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Restriction requirement/election

Election, with traverse, of the claims of Group II (encompassing claims 3-7, 9, 11, and 46-51), directed to polynucleotides, vectors, host cells, and methods of using the polynucleotides to produce the encoded polypeptides, is acknowledged. Applicants thank the Examiner for acknowledging that, upon allowance of the product claims, rejoinder of process claims commensurate in scope with the allowed product claims will be considered.

II. Objection to the specification

The specification was objected to based on an allegation that "it contains references to the tables that are not included in the disclosure. These tables are presented as separate entities" (Office Action, November 19, 2002; page 3).

Tables 1 through 7, having a total of 8 pages, were submitted with the specification, claims, abstract, and Sequence Listing on July 12, 2001, the filing date of the instant application (See, e.g., page 1 of the application Transmittal). Each of the tables is referenced in the specification (e.g., at page 7, lines 16-33). Therefore, Applicants believe that the tables are properly part of the disclosure of the application.

As the Office Action recognizes, the guidelines set out on pages 4-5 of the Office Action are for the **preferred** layout and content of patent applications, but there is no requirement that these guidelines be met. Thus, there is no basis for holding that the Tables are not a proper part of the disclosure of the application, and Applicants request withdrawal of this objection to the specification.

In the alternative, Applicants request that the Examiner indicate specific steps that the Applicants could take to include the tables into the disclosure in such a way as to satisfy the Examiner's requirements.

III. Claim objections

Claims 48-50 have been amended such that they further limit their respective base claims, as suggested by the Examiner. Withdrawal of this claim objection is therefore requested.

IV. Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 6, 7, 9, 11, and 48-51 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. The Office Action asserts that "neither the description of the structure and function of a DNA encoding SEQ ID NO:1 nor the disclosure solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus" (Office Action, November 19, 2002; page 6). This rejection is traversed

As discussed below, the recitation of structural features in the claims is enough to provide an adequate written description of polynucleotides encoding polypeptide variants and fragments of SEQ ID NO:1.

Nevertheless, to expedite prosecution, claim 3 has been amended such that the recited polypeptide variants and fragments have "cytochrome P450 activity." Support for these amendments can be found in the specification at, for example, page 70, line 21 to page 71, line 14. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides encoding polypeptide variants and fragments lacking cytochrome P450 activity. Applicants do not concede to the Patent Office position; Applicants are amending the claim solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that the claim, as amended, recites patentable subject matter.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" and "fragments" of SEQ ID NO:1 and SEQ ID NO:2.

The subject matter encompassed by claims 3, 6, 7, 9, 11, and 48-51 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 3 recites a polynucleotide encoding "a polypeptide comprising a naturally occurring amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has cytochrome P450 activity" and the "variant" language of independent claim 11 recites "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:2." Furthermore, the "fragment" language of independent claim 3 recites a polynucleotide encoding a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, "wherein the fragment has

cytochrome P450 activity, and wherein the fragment comprises contiguous residues P42-L499 of SEQ ID NO:1," and the "fragment" language of independent claim 52 recites a polynucleotide "comprising at least 750 contiguous nucleotides of the polynucleotide sequence of SEQ ID NO:2" or "comprising nucleotides 843-1582 of SEQ ID NO:2."

The amino acid sequence of SEQ ID NO:1 and the polynucleotide sequence of SEQ ID NO:2 are explicitly disclosed in the specification. See, for example, the Sequence Listing. Variants of SEQ ID NO:1 and SEQ ID NO:2 are described in the Specification at, for example, page 3, lines 9-14, 16-21, and 24-30; page 3, line 33 to page 4, line 3; page 4, lines 13-17 and 19-25; page 5, lines 6-12, 16-23, and 28-33; page 6, lines 5-10 and 14-19; page 8, lines 20-22; page 8, line 27 to page 9, line 14; page 19, lines 1-2; page 20, line 31 to page 21, line 20; page 23, lines 23-26; page 23, line 33 to page 24, line 24; page 26, lines 15-26; page 32, lines 3-5; page 33, lines 25-27; and page 50, lines 19-22. Fragments of SEQ ID NO:1 and SEQ ID NO:2 are described in the Specification at, for example, page 3, lines 9-14, 16-21, and 24-30; page 3, line 33 to page 4, line 3; page 4, lines 17-18 and 25-31; page 5, lines 6-12, 16-23, and 28-33; page 6, lines 5-10 and 14-19; page 8, lines 15-19; page 12, line 13 to page 13, line 2; page 16, lines 28-32; page 17, lines 5-6; page 17, line 23 to page 18, line 1; page 22, lines 31-34; page 24, line 25-32; page 26, lines 15-19; page 32, lines 26-27; page 33, lines 14-15; page 37, lines 2-15; page 51, lines 9-10; page 55, lines 17-20; page 58, lines 34-35; page 63, lines 32-34; page 67, lines 15-18; and page 69, lines 23-26. In addition, examples of fragments of SEQ ID NO:1 are provided, for example, in Table 3, and examples of fragments of SEQ ID NO:2 are provided, for example, in Table 4. Furthermore, specific assays to measure cytochrome P450 activity are disclosed in the Specification at, for example, page 70, line 21 to page 71, line 14.

One of ordinary skill in the art would recognize polynucleotide sequences which are variants having a polynucleotide sequence at least 95% or 98% identical to SEQ ID NO:2, or which encode polypeptide variants having an amino acid sequence at least 98% identical to SEQ ID NO:1. Given any naturally occurring polynucleotide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:2, or whether it encoded a variant of SEQ ID NO:1. Furthermore, it would be routine for one of skill in the art to determine whether any particular variant of SEQ ID NO:1 had cytochrome P450 activity, using the disclosed cytochrome P450 assays.

Accordingly, the specification provides an adequate written description of the recited polynucleotide variants of SEQ ID NO:2 and polynucleotides encoding polypeptide variants of SEQ ID NO:1.

One of ordinary skill in the art would recognize polynucleotide sequences which are fragments comprising at least 750 contiguous nucleotides of SEQ ID NO:2, or comprising nucleotides 843-1582 of SEQ ID NO:2, or which encode polypeptide sequences which are fragments comprising contiguous residues P42-L499 of SEQ ID NO:1. The information provided by SEQ ID NO:1 and SEQ ID NO:2 provides the necessary framework for the recited fragments -- to recite every possible fragment would needlessly clutter the application. Furthermore, it would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:1 had cytochrome P450 activity, using the disclosed cytochrome P450 assays. Accordingly, the specification provides an adequate written description of the recited polynucleotide fragments of SEQ ID NO:2, and polynucleotides encoding the recited fragments of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claims 3 and 11 recites chemical structure to define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has cytochrome P450 activity, and wherein the naturally occurring amino acid sequence comprises contiguous residues P42-L499 of SEQ ID NO:1, and
> c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has cytochrome P450 activity, and wherein the fragment comprises contiguous residues P42-L499 of SEQ ID NO:1.

11. An isolated polynucleotide selected from the group consisting of:
a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:2,
c) a polynucleotide complementary to a polynucleotide of a),
d) a polynucleotide complementary to a polynucleotide of b), and
e) an RNA equivalent of a)-d).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides. The polynucleotides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base the written description inquiry "on whatever is now claimed," the Patent Office failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for

assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polynucleotides encoding cytochrome P450 proteins, including polynucleotides encoding cytochrome P450 proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as cytochrome P450 proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polynucleotide encoding a polypeptide comprising "a naturally occurring amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 504 amino acid residues). This variation is far less than that of polynucleotides encoding all potential cytochrome P450 proteins related to SEQ ID NO:1, i.e., those cytochrome P450 proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 14, 2000. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject

application, the present inventors were in possession of the claimed polynucleotide variants and fragments at the time of filing of this application.

4. Summary

The Office Action failed to base the written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be withdrawn.

V. Enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 6, 7, 9, 11, 13, and 48-51 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed variants and fragments (Office Action, November 19, 2002; pages 7-9). In particular, the Office Action asserts that "the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially

infinite possible choices is likely to be successful" (Office Action, November 19, 2002; page 8; emphasis in original). Such, however, is not the case.

With respect to the claimed variants, note that claim 3, for example, recites not only that the polynucleotides encode polypeptides which are at least 98% identical to SEQ ID NO:1, but also that they have "**a naturally occurring amino acid sequence**." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of CYTPV) and SEQ ID NO:2 (the polynucleotide sequence encoding CYTPV), one of skill in the art would be able to routinely obtain "a naturally occurring amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., page 15, line 20 to page 16, line 21; page 17, line 23 to page 18, line 31; page 47, line 22 to page 48, line 4; and Example IX at pages 63-64. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:1, or vast numbers of polynucleotides based on the polynucleotide sequence of SEQ ID NO:2. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims using conventional techniques of recombinant protein production. By extension, one of skill in art could make fragments of naturally occurring polynucleotides at least 95% identical to SEQ ID NO:2, and could use such fragments, for example, as hybridization probes to detect full-length naturally occurring polynucleotides at least 95% identical to SEQ ID NO:2.

The Office Action asserts that "the claims encompasses DNAs encoding polypeptide having no known functions. The specification does not teach how to use said inactive variants" (Office Action, November 19, 2002; page 9). This is incorrect. One of skill in the art would reasonably conclude that

the claimed polynucleotides encode polypeptide variants having the functions of the polypeptide of SEQ ID NO:1. For example, Brenner et al. (Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078) teach that sequence homology as low as 30% over 150 amino acid residues, and as low as 40% over 70 amino acid residues, is indicative of protein homology. Furthermore, Bork (Genome Res., 2000, 10:398-400) teaches that the prediction of functional features by homology has a 90% accuracy rate, and that the accuracy rate for all bioinformatics predictions has a 70% accuracy rate (Table 1 of Bork). Thus, one of skill in the art would reasonably understand that a polypeptide "at least 98% identical" to SEQ ID NO:1 could be used in the same way as the polypeptide of SEQ ID NO:1.

Furthermore, it is irrelevant whether any of the claimed polynucleotides encode polypeptide variants which have "no known functions." One of skill in the art would still know how to make and use such polynucleotides, without undue experimentation. For example, polynucleotides which encode nonfunctional polypeptide variants of SEQ ID NO:1 could be used to detect polynucleotides which encode the polypeptide of SEQ ID NO:1 by, for example, hybridization and/or PCR techniques. It is not necessary for a polynucleotide to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide without undue experimentation.

Nevertheless, to expedite prosecution, claim 3 has been amended such that the recited polypeptide variants have "cytochrome P450 activity." Support for this amendment can be found in the specification at, for example, page 70, line 21 to page 71, line 14. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides encoding polypeptides lacking cytochrome P450 activity. Applicants do not concede to the Patent Office position; Applicants are amending the claim solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that the claim, as amended, recites patentable subject matter.

With respect to the claimed fragments, one of skill in the art could make and use the claimed polynucleotide fragments without undue experimentation, based on the Specification and the state of the art at the time the application was filed. For example, one of skill in the art would know how to use the claimed polynucleotide fragments as hybridization probes or PCR probes to detect the presence of a polynucleotide comprising SEQ ID NO:2 (Specification, e.g., at page 47, line 22 to page 48, line 4;

and Example IX at pages 63-64). As discussed above, it is not necessary for a polynucleotide fragment to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide without undue experimentation.

Furthermore, the Office Action seems to imply that the use of the transitional phrase "comprising" in the claims precludes enablement because one of skill in the art could not make and use polynucleotides encoding a polypeptide which included any possible element which could be a part of, but is not essential to, the claimed subject matter. The transitional phrase " '[c]omprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." M.P.E.P. § 2111.03. The specification has provided enablement for numerous examples of the recited polypeptides comprising immunogenic fragments of SEQ ID NO:1, such as fusion proteins and coupled proteins (Specification, e.g., at page 32, lines 3-20; page 37, lines 9-14; page 68, lines 7-18; and page 69, lines 23-26). One of skill in the art would understand how to make and use polynucleotides encoding the recited polypeptides comprising SEQ ID NO:1, without an explicit disclosure of how to make and use every possible element which could be a part of, but is not essential to, the claimed subject matter.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides encoding polypeptide variants and fragments of SEQ ID NO:1, or the recited polynucleotide variants and fragments of SEQ ID NO:2. Hence, a *prima*

facie case for non-enablement has not been established with respect to the recited variants and fragments of SEQ ID NO:1 and SEQ ID NO:2.

For at least the above reasons, withdrawal of this rejection is requested.

VI. Rejection under 35 U.S.C. § 112, second paragraph

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of the term "encoding" is indefinite. The Office Action asserts that "it is unclear whether 'encoding' is open or closed language. In other words, it is unclear whether a DNA encoding an immunogenic fragment, for example, can encode other sequences" (Office Action, November 19, 2002; page 10). This rejection is traversed.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir.1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

Claim 3 is drawn to polynucleotides "encoding" the recited polypeptides. One of ordinary skill in the art would reasonably understand that polynucleotides which "encode" a given polypeptide are those polynucleotides having a nucleotide sequence which can be translated into the amino acid sequence of the polypeptide based on, for example, the genetic code which forms the basis for life on Earth. This genetic code, which correlates triplets of nucleotides with amino acids, has been well known for decades, and forms the basis for humankind's understanding of molecular biology. The specification explicitly refers to this genetic code at, for example, page 24, lines 7-14:

> It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding CYPTV, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occuring CYTPV, and all such variations are to be considered as being specifically disclosed.

Thus, a skilled artisan would reasonably understand that the claimed polynucleotides encompass those which "encode" the recited polypeptides.

Furthermore, it is irrelevant whether a DNA which encodes one of the recited polypeptides "can encode other sequences." Claim 3 recites isolated polynucleotides encoding the recited polypeptides. The metes and bounds of the claimed polynucleotides are explicitly set out in the language of the claim. A skilled artisan would understand the metes and bounds of claim 3 based on the claim language, without having to do any further analysis of whether the claimed subject matter had properties not recited in the claim (e.g., such as the ability to "encode other sequences"). The question of whether the claimed polynucleotides "can encode other sequences" is simply not germane to the determination of the metes and bounds of the claimed invention.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

VII. Rejection of claims 3, 6, 7, 9, 11, and 48-51 under 35 U.S.C. § 102(b)

Claims 3, 6, 7, 9, 11, and 48-51 were rejected under 35 U.S.C. § 102(b) because the recited polynucleotides are allegedly anticipated by Hayashi et al. (EP 0 644 267 A2; March 22, 1995). The Office Action asserts that Hayashi et al teach "a DNA encoding human cytochrome P450 1A2 having the amino acid sequence that is 99.3% identical to SEQ ID NO:1, a vector containing it and a cell expressing thereof" (Office Action, November 19, 2002; page 10). This rejection is traversed.

Applicants respectfully disagree with the Patent Office position that the cytochrome P450 1A2 of Hayashi et al. is 99.3% identical to SEQ ID NO:1 of the instant application. While the Hayashi et al. cytochrome P450 1A2 may have 99.3% sequence identity to portions of SEQ ID NO:1, the sequence

identity over the entire length of these polypeptides is 97% (see, for example, Exhibit A). Therefore, the Hayashi et al. cytochrome P450 1A2 is not "99.3% **identical** to SEQ ID NO:1."

To expedite prosecution of claims 3, 6, 7, 9, and 48, claims 3 and 48 have been amended such that the recited polypeptide variants and fragments, which are encoded by the claimed polynucleotides, comprise "contiguous residues P42-L499 of SEQ ID NO:1." Support for these amendments can be found in the specification at, for example, Table 3. Table 3 of the specification indicates that the contiguous portion of SEQ ID NO:1 spanning residues P42-L499 is a cytochrome P450 consensus sequence, as determined by the HMMER program using the PFAM database. Table 7 of the specification provides the threshold parameters used in the analysis of SEQ ID NO:1 by the HMMER program using the PFAM database.

By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include variants and fragments of SEQ ID NO:1 which do not comprise contiguous residues P42-L499 of SEQ ID NO:1. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that claims 3 and 48, as amended, and dependent claims 6, 7, and 9, recite patentable subject matter. Therefore, withdrawal of this rejection with respect to claims 3, 6, 7, 9, and 48 is requested.

With respect to claims 11 and 50, the Office Action asserts that the DNA of Hayashi et al., which encodes a polypeptide that has 99.3% sequence identity to portions of SEQ ID NO:1, anticipates the recited polynucleotides. However, to support an anticipation rejection, there is a burden on the Patent Office to provide convincing proof that the references teach the claimed invention. In this case, the Patent Office has not met this burden. The Office Action has not shown **how** Hayashi et al. teach each and every element of the claimed polynucleotides. For at least this reason, withdrawal of this rejection with respect to claims 11 and 50 is requested.

Nevertheless, to expedite prosecution, claims 11 and 50 have been amended such that the recited polynucleotide variants comprise a naturally occurring polynucleotide sequence "at least 95% identical" or "at least 98% identical" to SEQ ID NO:2. Support for these amendments can be found in

the specification at, for example, page 20, line 31 to page 21, line 2. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides less than 95% identical to SEQ ID NO:2, or less than 98% identical to SEQ ID NO:2. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claims 11 and 50, as amended, recite patentable subject matter. Therefore, withdrawal of this rejection with respect to claims 11 and 50 is requested.

With respect to claims 49 and 51, the Office Action asserts that the DNA of Hayashi et al., which encodes a polypeptide that has 99.3% sequence identity to portions of SEQ ID NO:1, anticipates the recited polynucleotides. However, to support an anticipation rejection, there is a burden on the Patent Office to provide convincing proof that the references teach the claimed invention. In this case, the Patent Office has not met this burden. The Office Action has not shown **how** Hayashi et al. teach each and every element of the claimed polynucleotides. For at least this reason, withdrawal of this rejection with respect to claims 49 and 51 is requested.

Furthermore, the polynucleotides recited by claims 49 and 51 are not taught by Hayashi et al. Claim 49 recites polynucleotides at least **95%** identical to SEQ ID NO:2, and claim 51 recites polynucleotides comprising at least 750 **contiguous** nucleotides of SEQ ID NO:2. Hayashi et al. do **not** teach polynucleotides at least 95% identical to SEQ ID NO:2, or polynucleotides comprising at least 750 contiguous nucleotides of SEQ ID NO:2. Therefore, Hayashi et al. do not anticipate the polynucleotides of claims 49 and 51, and withdrawal of this rejection with respect to claims 49 and 51 is requested.

VIII. Rejection of claims 3, 6, 7, 9, and 48-51 under 35 U.S.C. § 102(b)

Claims 3, 6, 7, 9, and 48-51 were rejected under 35 U.S.C. § 102(b) because the recited polynucleotides are allegedly anticipated by Jaiswal et al. (GenBank Accession Z00036; September 12, 1993). The Office Action asserts that Jaiswal et al "teach a DNA encoding human cytochrome

P3(450) that is 93.6% identical to SEQ ID NO:2, a vector containing it and a cell expressing thereof" (Office Action, November 19, 2002; page 11). This rejection is traversed.

With respect to claims 3, 6, 7, 9, and 48, the Office Action asserts that the DNA of Jaiswal et al., which is 93.6% identical to SEQ ID NO:2, anticipates the recited polynucleotides. However, to support an anticipation rejection, there is a burden on the Patent Office to provide convincing proof that the references teach the claimed invention. In the case, the Patent Office has not met this burden. The Office Action has not shown **how** Jaiswal et al. teach each and every element of the claimed polynucleotides. For at least this reason, withdrawal of this rejection with respect to claims 3, 6, 7, 9, and 48 is requested.

Nevertheless, to expedite prosecution, claims 3 and 48 have been amended such that the recited polypeptide variants and fragments, which are encoded by the claimed polynucleotides, comprise "contiguous residues P42-L499 of SEQ ID NO:1." Support for these amendments can be found in the specification at, for example, Table 3. Table 3 of the specification indicates that the contiguous portion of SEQ ID NO:1 spanning residues P42-L499 is a cytochrome P450 consensus sequence, as determined by the HMMER program using the PFAM database. Table 7 of the specification provides the threshold parameters used in the analysis of SEQ ID NO:1 by the HMMER program using the PFAM database.

By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include variants and fragments of SEQ ID NO:1 which do not comprise contiguous residues P42-L499 of SEQ ID NO:1. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that claims 3 and 48, as amended, and dependent claims 6, 7, and 9, recite patentable subject matter. Therefore, withdrawal of this rejection with respect to claims 3, 6, 7, 9, and 48 is requested.

With respect to claims 49 and 51, the Office Action asserts that the DNA of Jaiswal et al., which is 93.6% identical to SEQ ID NO:2, anticipates the recited polynucleotides. However, to support an anticipation rejection, there is a burden on the Patent Office to provide convincing proof that

the references teach the claimed invention. In this case, the Patent Office has not met this burden. The Office Action has not shown **how** Jaiswal et al. teach each and every element of the claimed polynucleotides. For at least this reason, withdrawal of this rejection with respect to claims 49 and 51 is requested.

Furthermore, the polynucleotides recited by claims 49 and 51 are not taught by Jaiswal et al. Claim 49 recites polynucleotides at least **95%** identical to SEQ ID NO:2, and claim 51 recites polynucleotides comprising at least 750 **contiguous** nucleotides of SEQ ID NO:2. Jaiswal et al. do **not** teach polynucleotides at least 95% identical to SEQ ID NO:2, or polynucleotides comprising at least 750 contiguous nucleotides of SEQ ID NO:2. Therefore, Jaiswal et al. do not anticipate the polynucleotides of claims 49 and 51, and withdrawal of this rejection with respect to claims 49 and 51 is requested.

With respect to claim 50, the Office Action asserts that the DNA of Jaiswal et al., which is 93.6% identical to SEQ ID NO:2, anticipates the recited polynucleotides. However, to support an anticipation rejection, there is a burden on the Patent Office to provide convincing proof that the references teach the claimed invention. In this case, the Patent Office has not met this burden. The Office Action has not shown **how** Jaiswal et al. teach each and every element of the claimed polynucleotides. For at least this reason, withdrawal of this rejection with respect to claim 50 is requested.

Nevertheless, to expedite prosecution, claim 50 has been amended such that it recites polynucleotides at least **98%** identical to SEQ ID NO:2. Support for this amendment can be found in the specification at, for example, page 20, line 31 to page 21, line 2. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides less than 98% identical to SEQ ID NO:2. Applicants do not concede to the Patent Office position; Applicants are amending the claim solely to obtain expeditious allowance of the instant application.

While not conceding to the Patent Office position, it is believed that claim 50, as amended, recites patentable subject matter. Therefore, withdrawal of this rejection with respect to claim 50 is requested.

IX. Allowable subject matter

Applicants thank the Examiner for indicating that claims 4, 5, 46, and 47 would be allowable if rewritten in independent form (See pages 1 and 11 of the Office Action of November 19, 2002). Applicants believe that the base claims recite patentable subject matter, so withdrawal of this objection is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE GENOMICS, INC.

Date: Feb 19, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1 and 2 have been canceled, without prejudice or disclaimer.

Claims 3, 11, 46, and 48-51 have been amended as follows:

3. (Twice Amended) An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has cytochrome P450 activity, and wherein the naturally occurring amino acid sequence comprises contiguous residues P42-L499 of SEQ ID NO:1, and

c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein [said] the fragment has cytochrome P450 activity, and wherein the fragment comprises contiguous residues P42-L499 of SEQ ID NO:1

[d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1].

11. (Once Amended) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least [90%] 95% identical to the polynucleotide sequence of SEQ ID NO:2,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

46. (Once Amended) A polynucleotide of claim 11, selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide complementary to the polynucleotide of a), and

c) an RNA equivalent of a)-b).

48. (Once Amended) A polynucleotide of claim 3, encoding a polypeptide comprising [an] a naturally occurring amino acid sequence at least 98% identical to the amino acid sequence of SEQ ID NO:1, wherein the polypeptide has cytochrome P450 activity, and wherein the naturally occurring amino acid sequence comprises contiguous residues P42-L499 of SEQ ID NO:1.

49. (Once Amended) A polynucleotide of claim 11, selected from the group consisting of:

a) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide complementary to the polynucleotide of a), and

c) an RNA equivalent of a)-b).

50. (Once Amended) A polynucleotide of claim 11, selected from the group consisting of:

a) a polynucleotide comprising a naturally occurring polynucleotide sequence at least [90%] 98% identical to the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide complementary to the polynucleotide of a), and

c) an RNA equivalent of a)-b).

51. (Twice Amended) An isolated polynucleotide of claim 52, [comprising at least 750 contiguous nucleotides of a polynucleotide] selected from the group consisting of:

a) a polynucleotide [consisting of] comprising at least 750 contiguous nucleotides of the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide complementary to the polynucleotide of a), and

c) an RNA equivalent of a)-b).

New claims 52-53 have been added as follows:

52. (New) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising at least 750 contiguous nucleotides of the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising nucleotides 843-1582 of SEQ ID NO:2,

c) a polynucleotide complementary to the polynucleotide of a),

d) a polynucleotide complementary to the polynucleotide of b), and

e) an RNA equivalent of a)-d).

53. (New) An isolated polynucleotide of claim 52, selected from the group consisting of:

a) a polynucleotide comprising nucleotides 843-1582 of SEQ ID NO:2,

b) a polynucleotide complementary to a polynucleotide of a), and

c) an RNA equivalent of a)-b).